USEPA (2016) further concludes that the laboratory animal evidence for EtO carcinogenicity is "sufficient" based on findings of tumors at multiple sites, by both oral and inhalation routes of exposure, and in both sexes of both rats and mice. Tumor types resulting from inhalation exposure included mononuclear cell leukemia in male and female rats and malignant lymphoma and mammary carcinoma in female mice, suggesting some site concordance with the lymphohematopoietic and breast cancers observed in humans, also exposed by inhalation. Lastly, USEPA concludes that the evidence of EtO genotoxicity and mutagenicity is unequivocal (see Section 3.5.1 of USEPA 23016 for details), ultimately classifying EtO as "*carcinogenic to humans*" under USEPA (2005a).

The TCEQ agrees that since the epidemiological evidence is less than convincing, additional lines of evidence are required for the EtO carcinogenic classification. USEPA (2016) cites the following lines of evidence to support the "*carcinogenic to humans*" classification: (1) there is strong, although less than conclusive on its own, evidence of cancer in humans associated with EtO exposure via inhalation, specifically, evidence of lymphohematopoietic cancers and female breast cancer in EtO-exposed workers; (2) there is extensive evidence of EtO-induced carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure; (3) EtO is a direct-acting alkylating agent whose mutagenic and genotoxic capabilities have been well established in a variety of experimental systems, and a mutagenic mode of carcinogenic action has been identified in animals involving the key precursor events of DNA adduct formation and subsequent DNA damage, including point mutations and chromosomal effects; and (4) there is strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage, such as chromosomal aberrations, SCEs, and micronuclei in EtO-exposed workers. In supporting a "*carcinogenic to humans (Group 1)*" designation, IARC (2012) draws conclusions similar to those of USEPA (2016), citing *limited evidence* in humans, *sufficient evidence* in experimental animals, and *strong evidence* supportive of a genotoxic MOA for carcinogenicity.

As mentioned in Section 3.3, the TCEQ has adopted the USEPA (2016) EtO carcinogenic classification (*carcinogenic to humans*) for purposes of this DSD.

3.4 Carcinogenic Dose-Response Assessment

Per TCEQ guidelines (TCEQ 2015), when toxicity factors or guideline air levels are identified in the scientific literature or databases, they are reviewed to determine whether the approaches used to develop the toxicity factors or guideline levels are similar to the procedures used by the TCEQ. If so, after careful consideration the TCEQ may elect to adopt the published toxicity factor or guideline level. In the present case, the scientific literature search identified USEPA (2016) and Valdez-Flores et al. (2010) as representing two relatively recent carcinogenic dose-response assessments for EtO for consideration under TCEQ guidelines (TCEQ 2015). In Sections

3.4.1.1 and 3.4.1.2 below, the TCEQ reviews the available data for MOA, endogenous EtO levels, key epidemiological data, and model predictions to determine whether to adopt the USEPA (2016) EtO inhalation URF. After making the adoption determination, the TCEQ continues with an original assessment to derive an EtO inhalation URF based on TCEQ guidelines and best principles.

3.4.1 Low-Dose Extrapolation Approach

Use of MOA information to inform the dose-response assessment is a main focus of the TCEQ (2015) and USEPA (2005a,b) guidelines. Consequently, examining the MOA (as well as dose-response) for cancer endpoints with statistically significant increases (e.g., endpoint-specific SMRs) is an important initial step in cancer dose-response assessment. Generally, the MOA and other information may support one of the following low-dose extrapolation approaches: (1) nonthreshold (typically a linear extrapolation to zero); (2) threshold (typically identifying a point of departure (POD) and applying uncertainty factors); or (3) both (TCEQ 2015). Thus, to the extent that an MOA for a chemical is understood, it informs the low-dose extrapolation procedure for that chemical. Examples of different shapes of dose-response curves are shown in Figure 1.

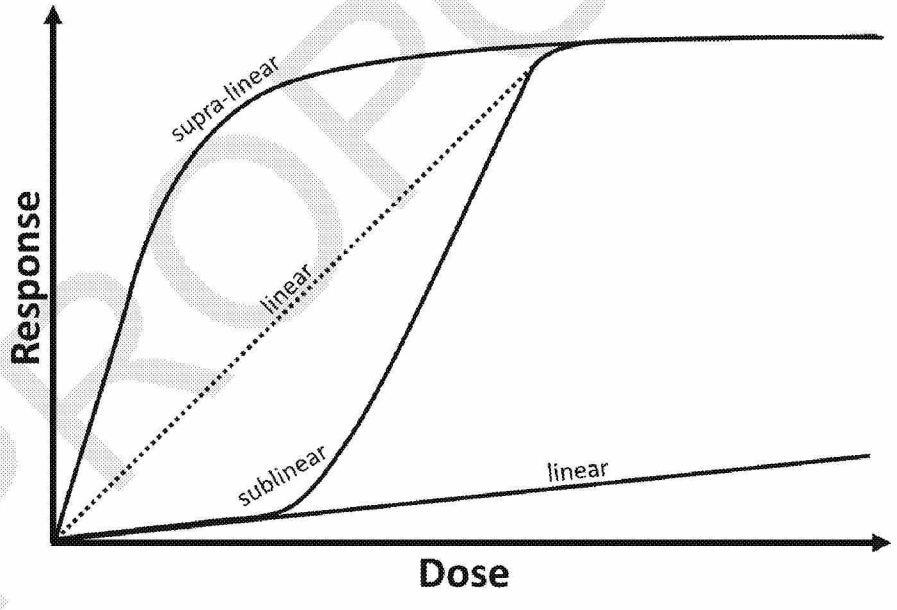

Figure 1: Dose-Response Curve Examples

One of the potential non-threshold dose-response curves shown in Figure 1 is supra-linear, with a steep low-dose slope. Section 7.7.7.3 of TCEQ (2015) addresses the potential use of a supra-linear dose-response model specifically, and indicates [*emphasis added*]:

> As indicated by Crump and Allen (1985), linear exposure-response models are "considered conservative in the sense that other biologically plausible dose-response models would generally imply lower risks." *Some researchers have published dose-response models that are inherently supra-linear at low exposures*. The increase of the hazard rate or relative risk of a supra-linear exposure-response model is faster at lower exposures than at higher exposures. *These types of models are generally not biologically plausible and tend to grossly exaggerate the estimation of risks at low exposures.*

The TCEQ guidelines (2015) go on to state... *"Using supra-linear exposure-response models can only be justified if there is sufficient biological or mechanistic data to support their application."* Another way to state this more specifically might be [*added*]... "Using *the initial steep slope starting at zero dose in* supra-linear exposure-response models can only be justified if there is sufficient biological or mechanistic data to support their application."

In this evaluation, the TCEQ concludes that the low-dose extrapolation of EtO-induced carcinogenic effects should be based on a model that is no more than linear, and arguably sublinear at endogenous levels and below. This conclusion is based on data relevant to the MOA, data on normal background endogenous EtO levels, key epidemiological study data (e.g., overall results for the UCC and NIOSH cohorts, doses associated with statistically increased cancer), and an evaluation of the ability of a model (or lack thereof) to reasonably predict the underlying dose-response data. *In contrast, USEPA (2016) used an overall supra-linear two-piece spline model for EtO carcinogenesis. This model assumed a non-threshold steep linear relationship between EtO and cancer formation at lower concentrations, with a high-concentration linear relationship that had a much shallower slope (i.e., an overall supra-linear relationship; similar to that depicted in Figure 1). In the present case, the TCEQ finds insufficient data to justify the supra-linear modeling approach (i.e., use of the steep lower-dose slope starting at zero dose from the linear two-piece spline model) ultimately adopted by USEPA (2016).* Even ignoring critical deterministic considerations (e.g., the lack of mechanistic data to justify use of an overall supra-linear model), as a much lesser secondary matter, the appropriate consideration of model fit criteria (e.g., for lymphoid cancer mortality in the NIOSH cohort) still does not support use of a supra-linear model over more conventional models (e.g., the likelihood of the linear two-piece spline model for lymphoid cancer mortality is not different from the likelihood of the null model at the 5% significance level, visual examination of model fits to the actual underlying data, etc.). These considerations are discussed in more detail below.

3.4.1.1 Consideration of MOA

MOA information is discussed in Section 3.3.1, which supports a likely mutagenic MOA for EtO carcinogenicity. *MOA information can suggest the likely shape of the dose-response curve at*

lower doses (USEPA 2005a). That is, toxicological principles can inform expectations about low-dose risk when truly low-dose data are unavailable. In this case, in the key epidemiological cohort (NIOSH) used by USEPA (2016), estimated mean worker exposures to EtO were ≈1,000,000-2,000,000 times higher than central tendency ambient environmental EtO levels (see Section 3.2.1.1). Consideration of a direct acting DNA-reactive chemical in conjunction with normal detoxification processes and baseline levels of DNA repair enzymes that have evolved to efficiently detoxify and/or repair significant levels of endogenous EtO and associated adducts (in the endogenous range) suggests a no more than linear low-dose response component near the endogenous range with a transition to a higher dose-response slope at some point above the endogenous range where the body can no longer effectively detoxify EtO and/or repair the resulting damage. Thus, across a range of doses from truly low (e.g., ambient air, endogenous) to high (e.g., high occupational exposures), the expected dose-response could be characterized as appearing sublinear in the low-dose range and/or sublinear overall across doses (see Figure 1). In contrast to the sublinear response associated with impaired detoxification and/or DNA repair for direct acting chemicals such as EtO, supra-linear responses are associated with an MOA that involves the saturation of metabolic activation where fewer electrophiles are formed per unit dose at higher exposures, which is not the case for EtO (Swenberg et al. 2008).

Kirman and Hays (2017) expressed this conclusion similarly. That is, based on relevant considerations, an overall sublinear (not supra-linear) dose-response would be expected over the range of possible exposures to EtO, from those that result in total body burdens (endogenous + exogenous) within the normal endogenous level range to those that result in a total body burden significantly greater than the normal range where the normally effective detoxification/repair processes are overwhelmed. This conclusion is reasonably consistent with that of the USEPA [*emphasis added*], "EPA considers it *highly plausible that the dose-response relationship over the endogenous range is sublinear* (e.g., that the baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work more effectively for lower levels of endogenous adducts), that is, that the slope of the dose-response relationship for risk per adduct would increase as the level of endogenous adducts increases." Figures 4 and 7 in Section 3.4.1.2.2 show that *EtO exposures corresponding to 1E-06 to 1E-04 excess risk based on USEPA (2016) are well below those corresponding to normal endogenous background levels*, inevitably leading to the expectation of sublinearity (or no excess risk) at such low doses based on the discussions above. In contrast to an overall linear or sublinear model, *using an overall supra-linear dose-response model (i.e., the steep low-dose component) to extrapolate risk down to an exposure lower than the point where a transition to a sublinear dose-response would be expected is not scientifically defensible and would be expected to grossly exaggerate truly low-dose risk (e.g., at endogenous levels and below).* That is, a steep slope from one portion of an overall supra-linear dose-response model should not be applied to a portion of the dose-response that admittedly is highly likely to have a shallow/sublinear slope.

Lastly, in addition to USEPA citing direct mutagenic activity as mechanistic justification for default linear extrapolation from high-to-low doses (pp. 4-22 and 4-37 of USEPA 2016) while still considering it "highly plausible that the dose-response relationship over the endogenous range is sublinear," *it is also critical to note that USEPA acknowledges the lack of mechanistic data to support the biological plausibility of an overall supra-linear dose-response, stating "the EPA is not aware of a mechanistic explanation" in response to questions from the USEPA SAB* (p. I-29 of USEPA 2016).

In summary:

- An overall sublinear dose-response is expected for endogenous, direct-acting chemicals like EtO (i.e., an overall more-than-/supra-linear dose-response is not expected).
- USEPA acknowledges that it is *highly plausible* that the EtO dose-response relationship over the endogenous range is *sublinear*, and since the exposures corresponding to 1E-06 to 1E-04 excess risk based on USEPA (2016) are *well below* those corresponding to normal endogenous background levels (see Figures 4 and 7 in Section 3.4.1.2.2), a sublinear dose-response would be expected at such low doses (if any biologically meaningful response is to be expected).
- Consequently, *it is not scientifically defensible and likely grossly exaggerates EtO low-dose risk to use a supra-linear dose-response model (i.e., the steep low-dose slope) to extrapolate risk below the point where a transition to a sublinear dose-response is expected or "highly plausible" (e.g., at endogenous levels and below).*
- As body burdens progressively increase to significantly higher levels than the normal endogenous range, excess risk is expected to increase as the normally relatively effective detoxification/repair processes are progressively overwhelmed at higher and higher doses, *making higher-than-endogenous risk increasingly discernable from background risk consistent with the assessment of "excess" (i.e., above background) risk.*

USEPA should not have used an overall supra-linear model (i.e., the linear two-piece spline model) to derive a URF for EtO without a robust mechanistic justification for expecting supra-linearity (i.e., the steep lower-dose slope component) at truly low doses or used it to make a large low-dose extrapolation through and below an area (i.e., the endogenous range) where the agency actually considers sublinearity as "highly plausible." The NIOSH data are, in fact, not inconsistent with such expectations at low doses of EtO as there are no truly low-dose data available from the cohort (Section 3.2.1.1).

3.4.1.2 Consideration of Endogenous Levels, Key Epidemiological Data, and Model Predictions

3.4.1.2.1 Endogenous Levels

The analysis of Kirman and Hays (2017) documents endogenous EtO levels normally found within the body expressed in terms of exogenous EtO exposures. Such information can provide support for a given risk assessment approach for chemicals such as EtO that have both endogenous and exogenous exposure pathways. Hemoglobin N-(2-hydroxyethyl)-valine (HEV) adducts are caused by the reaction of EtO with hemoglobin in erythrocytes and provide a biomarker/molecular dosimeter of internal EtO dose that can be correlated with exogenous (i.e., ambient air) EtO exposure. USEPA (2005a) indicates that it may be informative to use such biomarkers of internal exposure for dose-response assessment or to provide insight into the potential shape of the dose-response curve at doses below those at which tumors are induced experimentally. As EtO is widely distributed in the body, the levels of HEV in erythrocytes are expected to be proportional to levels of HEV in other tissues (including target tissues), which are further expected to be proportional to tissue exposures to free EtO (Kirman and Hays 2017). Kirman and Hays (2017) conducted a meta-analysis from the published literature characterizing the distribution of HEV adducts in EtO-unexposed (i.e., the background endogenous distribution) and exposed populations (smokers, workers). The relationship between exposure and HEV adducts is linear with R^2=0.998 (see Figure 3 of the study). In the meta-analysis for unexposed populations (n=661), the weighted mean of background endogenous HEV (random effects model) was 21.1 pmol/g Hb with a standard deviation (SD) of 14.6 pmol/g Hb. The fixed effects model produced very similar results (see Table 3 of the study).

The TCEQ further evaluated the unexposed population data (n=661) and determined that an increase in the mean HEV of ≥0.861 pmol/g Hb would be statistically significant ($p \leq 0.05$, Appendix 2). This HEV increase would correspond to continuous environmental air concentrations of ≈ ≥0.08 ppb. While continuous exposure of this unexposed population to EtO concentrations ≥0.08 ppb would be expected to cause a statistically significant increase in HEV (≥0.861 pmol/g Hb), there is no basis to conclude that such a change would be biologically significant. For example, the addition of 0.861 pmol/g Hb represents less than 5% of the mean and such a deviation appears to be well within the range of normal endogenous variation (e.g., SD = 14.6 pmol/g Hb; 5th to 95th percentile range = 6.1-48.7 pmol/g Hb; Table 4 of Kirman and Hays 2017). A statistically significant change that lacks biological significance is not considered an adverse response (TCEQ 2015).

A 1 SD change from the mean is considered as a critical effect size (CES) for potentially adverse continuous endpoints (TCEQ 2015) in the absence of a CES that distinguishes between levels of change that should be considered biologically significant or adverse and those that should not (i.e., absent a commonly accepted bright line demarcation). That being said, DNA and/or

protein (e.g., HEV) adducts are not usually used by environmental regulatory agencies to derive regulatory values because such adducts do not clearly meet the typical regulatory definition of "adverse effect" (i.e., a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge). Rather, protein adducts such as HEV may simply be viewed as biomarkers of internal exposure that can be related back to external exposure levels in the present case. Accordingly, applying this 1 SD CES approach to continuous endpoint changes, particularly normal endogenous background levels, that do not clearly meet the typical regulatory definition of "adverse" may be considered conservative. Nevertheless, this analysis provides some needed context in this case. With that in mind, the continuous EtO exposure corresponding to an increase of 1 SD in HEV (14.6 pmol/g Hb) is ≈1.3 ppb (Table 4 of Kirman and Hays 2017). This does not provide a basis for expecting a biologically-significant/meaningful increase in internal exposure with continuous exposure to < 1 ppb EtO because a > 1 ppb continuous exposure is required to produce a 1 SD increase in HEV levels (which this example is conservatively considering as both statistically significant and potentially biologically significant). *Rather, these considerations suggest that inhalation exposure to sub-ppb EtO air concentrations (particularly parts per trillion (ppt) concentrations such as 0.1-10 ppt) is of little biological importance compared to normal endogenous background levels.* Considering EtO as a mutagenic carcinogen, this is generally consistent with the conclusions of Swenberg et al. (2008) that:

1) At low exposures, the likelihood that a mutation will arise from exogenous adducts becomes *de minimus* as compared to the large molecular dose normally formed endogenously (e.g., *Hprt* mutations were not statistically increased compared to background in mice exposed even up to 10 ppm EtO; high exposure to ≥50 ppm EtO was required to produce statistically significant increases over background; see Figure 9 of the study); and
2) The biologic effects of *de minimus* exposures below endogenous amounts are lost in the noise of the background (e.g., carcinogenesis is driven by endogenous DNA damage when the dose-response for mutations due to external EtO exposure comes into the normal background frequency due to endogenous production).

Put another way by Kirman and Hays (2017), pragmatically speaking, the considerable variation in endogenous EtO exposure creates a signal-to-noise issue when exogenous exposures fall well below those consistent with endogenous exposures, and in such cases small exogenous exposures may not contribute to total exposure or to potential effects in a biologically meaningful way.

Lastly, endogenous/background level data can be used for a reality check on the USEPA (2016) lymphoid cancer URF. Use of the EtO air concentration corresponding to the mean of normal

endogenous background levels in the unexposed population (1.9 ppb) in conjunction with the USEPA (2016) age-dependent adjustment factor (ADAF)-adjusted URF for lymphoid cancer (7.1E-03 per ppb) suggests a background incidence of ≈1.35% in nonsmokers due to endogenous EtO alone, which remarkably would be almost half (46%) of the lymphoid cancer background incidence of 3% (p. 4-95 of USEPA 2016). However, the smoking population must also be considered. Use of the EtO air concentration corresponding to the mean background in smokers (18.8 ppb at an HEV of 205.4 pmol/g Hb; Tables 2 and 4 of Kirman and Hays 2017) with the lymphoid cancer URF suggests an incidence of lymphoid cancer in smokers of ≈13.3% due to EtO alone. *Weighting the URF-estimated lymphoid cancer incidence for smokers (13.3%) at 20.9% of the population (for 2005 since current cancer rates would reflect contributions from past smoking, generally consistent with the USEPA 2016 exposure lag period of 15 years) with that for nonsmokers (1.35%) results in a population estimate of ≈3.85% due to background EtO levels in the U.S. population alone (e.g., without contributions from EtO in ambient air, contributions from the endogenous conversion of ethylene to EtO, known chemical leukemogens, or other risks factors such as genetic predispositions), which is higher than the lymphoid cancer background incidence of 3% cited by USEPA (p. 4-95 of USEPA 2016). This reality check suggests a scientifically unreasonable URF.*

In regard to the endogenous conversion of exogenous ethylene to EtO, USEPA may not have adequately explored the potential contributions of ethylene exposure to EtO risk, stating "only ≈3% of exogenous ethylene was converted to EtO in workers exposed to 0.3 ppm" and that "exogenous ethylene exposure is unlikely to contribute significantly to the effects associated with exposure to exogenous EtO in humans" (p. 3-30 of USEPA 2016). *However, based on USEPA's URF, mean environmental concentrations of ethylene in many areas would in fact result in unacceptable excess risk estimates when multiplied by 0.03 to account for the USEPA-cited endogenous conversion of 3% of exogenous ethylene to EtO.* More specifically, greater than a 1E-04 excess risk would be estimated by USEPA's EtO URF at long-term ethylene air concentrations greater than 0.37 ppb (i.e., 0.37 ppb ethylene × 0.03 converted-to-EtO = 0.011 ppb EtO × 9.1E-03 per ppb = 1.0E-04). For additional context, this concentration is not only exceeded by ambient levels in many areas, but also by the indoor mean range (0.82-3.3 ppb) and personal exposure mean range (3.1-3.6) provided by Health Canada (2016). Interestingly, mean ethylene concentrations reported in human breath (e.g., 23 ppb in Fenske and Paulson 1999, 29-32 ppb reported in Bratu 2019) exceed this 1E-04 excess risk concentration (0.37 ppb ethylene based on USEPA 2016) by over 60-fold.

Data on normal endogenous background levels of EtO are also used in the next section, in conjunction with relevant epidemiological data.

3.4.1.2.2 Key Epidemiological Data with Additional Context Using Endogenous Data and Model Predictions

Key epidemiological findings were reviewed for consistency with expectations for an overall supra-linear dose-response for EtO-induced carcinogenicity. *If the underlying dose-response for EtO-induced cancer in humans were supra-linear with a steep low-dose slope beginning at zero dose, statistically significant increases in critical cancer endpoints would be expected beginning in the lower occupational exposure groups*. That is, if exogenous EtO had a steep dose-response slope (i.e., were a potent carcinogen) starting in the true low-dose region, such as near the range of endogenous levels (as modeled in USEPA 2016), then statistically increased cancer mortality rates would be expected at the "low" worker doses evaluated for large cohorts (NIOSH, UCC), particularly considering that even "low" historical worker exposures have been significantly higher than environmental EtO concentrations (statistically confirmed; see Section 3.4.1.2.2.3). For example, in regard to the NIOSH cohort, Tables IV and V of Hornung et al. (1994) provide measured and estimated worker EtO exposure means (3.5-4.6 ppm) that are ≈1,000,000-2,000,000 times higher than central tendency environmental levels (≈0.0024-0.0034 ppb per USEPA 2016). Remarkably, estimated daily EtO exposure for a job could have ranged from ≈15,000-32,000,000 times the central tendency environmental levels (see Section 3.2.1.1). Mean NIOSH cohort exposure levels of 3.5-4.6 ppm, for example, are over 1,800-2,400 times higher than mean normal endogenous background and about 500-700 times higher than even the 99th percentile of normal endogenous background (Table 4 of Kirman and Hays 2017). For the UCC cohort, the average cumulative EtO exposure was twice as high as that for the NIOSH cohort (although the study power is less; see Section 3.2.1.2). *Thus, considering significantly elevated historical occupational exposures, if EtO-induced cancer had a steep dose-response slope (i.e., were a potent carcinogen) in the true low-dose region (as modeled in USEPA 2016), then the epidemiological evidence for cancer in workers induced by this direct-acting mutagenic carcinogen would be expected to be conclusive, for both males and females, but is not.* For example, regarding the epidemiological evidence, USEPA (2016) states that while there is "*some* evidence of dose-response relationships", "there is *little strength* in the associations." This certainly would not be expected for a potent low-dose human carcinogen with a steep low-dose slope (as part of the overall supra-linear dose-response) when there was significantly elevated historical occupational exposure, but nevertheless is why USEPA (2016) and the TCEQ must partially rely on animal data for a finding of "carcinogenic to humans." Below, key epidemiological data, alone and in conjunction with data on normal endogenous background levels, are further reviewed to determine if this information is supportive of adoption of a supra-linear dose-response (i.e., the steep low-dose component) for low-dose extrapolation of carcinogenic risk for EtO.

3.4.1.2.2.1 Key Data from the UCC Cohort

Multiple analyses of epidemiological data from the UCC cohort have shown no long-term carcinogenic effects associated with EtO exposure. Swaen et al. (2009) reported no indications of excess cancer risk, including for the lymphohematopoietic malignancies. There were no trends or associations with cumulative exposure for all cause, leukemia, or lymphoid malignancy mortality. Additionally, no statistically significantly elevated SMRs were found in the analysis by hire date, there were no statistically significant increases in the longest duration category, and no suggested trends by duration (all surrogates of exposure). *Likewise, an update of the UCC cohort through 2013 (unpublished as of the date of this DSD) concludes that examination of mortality from all causes of death, all cancers, leukemia, non-Hodgkin's lymphoma, and lymphoid malignancies revealed no evidence for an exposure-related response. EtO exposure in this cohort (with average cumulative dose of ≈67 ppm-years and average follow-up of ≈41 years) was not associated with an observable increase in lymphohematopoietic cancer mortality* (personal communication with study co-author Ciriaco Valdez-Flores). These UCC study results in highly-exposed workers are not consistent with EtO-induced carcinogenicity, much less a supra-linear dose-response with a steep low-dose component (e.g., USEPA's linear two-piece spline model).

3.4.1.2.2.2 Key Data from the NIOSH Cohort and Endogenous Data

Regarding key epidemiological data, this section primarily focuses on statistically significant cancer endpoint increases with EtO exposure in the most sensitive sex (male or female) in the NIOSH cohort, although combined results (male + female) are also discussed. Tables 4 and 5 contain the lowest male or female dose group with a statistically significant increase for each critical cancer endpoint in the cohort based on evaluations by Valdez-Flores et al. (2010) and Steenland et al. (2004, 2003), respectively. Columns 1 and 4 of Table 4 show that based on the analyses in Valdez-Flores et al. (2010), critical cancer endpoints in the NIOSH cohort (i.e., lymphohematopoietic, lymphoid, non-Hodgkin's lymphoma) were only statistically increased in males, and only in the highest (5^{th}) EtO exposure quantile. Breast cancer in females was not statistically increased even in the highest exposure group (5^{th} quantile). The upper ends of the exposure intervals for these highest (5^{th}) quantiles are open ended, and even the lower ends of the exposure intervals are extraordinarily high. *It is remarkable that although workers were exposed to EtO air concentrations ≈15,000-32,000,000 times higher than central tendency environmental levels, critical cancer endpoints such as lymphoid cancer mortality were only statistically increased in the highest male exposure group. Such high occupational exposures being required to produce statistically significant increases in a large cohort is not consistent with a steep dose-response slope beginning at zero dose in the low-dose region of a supra-linear dose-response (e.g., in the range of endogenously- or environmentally-relevant doses).* Importantly, Table 4 also utilizes data from Kirman and Hays (2017) to calculate environmental EtO exposures (ppm-days) corresponding to the normal endogenous background range (column 2), and then converts those environmental exposures to equivalent occupational exposures

(column 3) for comparison to the occupational carcinogenic doses (ppm-days) for critical cancer endpoints (i.e., occupational doses associated with statistically increased cancer). The comparisons provided in column 5 of Table 4 show that across statistically increased cancer endpoints (excludes breast cancer), the lowest carcinogenic doses for EtO (ppm-days, unlagged) in either sex are:

- ≈500-800 times higher than the mean endogenous background EtO dose in the unexposed population;
- ≈600-900 times higher than the median endogenous background EtO dose in the unexposed population;
- ≈1,600-2,700 times higher than the 5th percentile of normal endogenous background EtO doses in the unexposed population; and
- ≈200-300 times higher than even the 95th percentile of normal endogenous background EtO doses in the unexposed population.

The bottom of Table 4 shows that on average, the lower ends of the carcinogenic doses for the most sensitive sex across endpoints are ≈600 higher than the mean endogenous background EtO dose in the unexposed population, ≈700 higher than the median endogenous background EtO dose, ≈2,100 higher than the 5th percentile of normal endogenous background EtO doses, and ≈300 times higher than the 95th percentile of normal endogenous background EtO doses in the unexposed population (Table 4).

Similarly, columns 1 and 4 of Table 5 show that based on the analyses in Steenland et al. (2004, 2003), certain critical cancer endpoints in the NIOSH cohort (i.e., all hematopoietic, lymphoid, non-Hodgkin's lymphoma) were only statistically increased in males, while breast cancer incidence was only statistically increased in females, and only in the highest EtO exposure quantiles for each of these cancer endpoints. The upper ends of the exposure intervals for these highest quantiles are open ended, and even the lower ends of the exposure intervals for these significantly lagged exposures (typically 15 years) are still remarkably high. High occupational EtO exposures being required to produce statistically significant increases in a large cohort is not consistent with the steep low-dose slope of a supra-linear dose-response starting at zero dose (e.g., across much lower and more environmentally-relevant exposures). The comparisons provided in column 5 of Table 5 show that on average, these lagged carcinogenic doses are:

- ≈90 times higher than the mean endogenous background EtO dose in the unexposed population;
- ≈100 times higher than the median endogenous background EtO dose in the unexposed population;

- ≈300 times higher than the 5th percentile of normal endogenous background EtO doses in the unexposed population; and
- ≈40 times higher than even the 95th percentile of normal endogenous background EtO doses in the unexposed population.

These differences are appreciable considering that the occupational exposures used for these comparisons have been reduced by lagging the exposure 10-15 years, and by using the lowest end of the carcinogenic dose range for each endpoint.

Based on the data in Tables 4 and 5 (as well as data from the cited source studies), Figures 2, 3, 4 and Figures 5, 6, 7 (Figures 3 and 6 in particular, with a log scale for the x- and y-axis) help demonstrate the significant difference between EtO doses corresponding to the normal endogenous background range (5th-95th percentile) and those associated with (and not associated with) statistically significant increases in the most sensitive sex for critical cancer endpoints in the NIOSH cohort (Valdez-Flores et al. 2010, Steenland et al. 2004, 2003). Figures 4 and 7 help to put into perspective the large differences between occupational EtO doses (ppm-days) and doses corresponding to 1E-06 to 1E-04 excess risk based on USEPA (2016) (i.e., 0.0001-0.01 ppb environmental converted to occupational ppm-days), those corresponding to normal endogenous background levels, and those associated with statistically significant increases in risk. *EtO doses at 1E-06 to 1E-04 excess risk based on USEPA (2016) are orders of magnitude below both those corresponding to normal endogenous background levels and those associated with statistically significant cancer increases in the NIOSH cohort.* Additionally, as shown in Figure 7, although USEPA considers it "*highly plausible* that the dose-response relationship over the endogenous range is *sublinear*," USEPA (2016) applied remarkably steep *supra-linear* model low-dose slopes for lymphoid and breast cancer (see Figures 4-9 and 4-10 of USEPA 2016) in the very region where sublinearity is expected (i.e., ≤ the normal endogenous background range). One consequence is that the EtO air concentration at even the maximum acceptable excess risk (0.01 ppb at 1E-04 risk) is over 30 and 50 times lower than air concentrations corresponding to the 1st and 5th percentile of normal endogenous background levels, respectively (e.g., 0.56 ppb at the 5th percentile (Table 4 of Kirman and Hays 2017) / 0.01 ppb at 1E-04 risk = 56-fold higher). Put another way, the USEPA considers EtO air concentrations corresponding to more than ≈0.5% percent of mean normal endogenous in nonsmokers to be associated with unacceptable risk (i.e., 0.01 ppb/1.9 ppb corresponding to the mean endogenous in nonsmokers (Table 4 of Kirman and Hays 2017) × 100 = 0.53%).

In regard to combined (male + female) results, although there were no statistically significant increases in mortality in female workers alone for any critical cancer endpoint in any cumulative EtO exposure group of the NIOSH cohort, combining data from male and female workers results in statistically significant increases for lymphohematopoietic and lymphoid cancer mortality at lower cumulative exposures than when evaluated on a sex-specific basis. For example, although

Steenland et al. (2004, 2003) is the source for Table 5, USEPA (2016) had additional analyses conducted for males + females (15-year exposure lag) that showed statistically increased lymphohematopoietic cancer mortality beginning at ≈2,440 ppm-days (midpoint of the 3rd EtO exposure quintile), and increased lymphoid cancer mortality at ≈2,440 ppm-days (midpoint of the 3rd quintile) and ≥13,500 ppm-days (lower end of 5th quintile) (Table 4-2 of USEPA 2016). Similarly, Valdez-Flores et al. (2010) conducted analyses for males + females (no exposure lag) that showed statistically increased lymphoid cancer mortality at ≈2,300 ppm-days (2nd EtO exposure quintile midpoint) and ≥47,559 ppm-days (5th quintile lower end) (Table S.9 of the study). While an explanation of the differences in results for the most sensitive sex versus combined analyses is beyond the scope of this DSD, it is noted that the lower end of these lagged/unlagged carcinogenic EtO doses for NIOSH males + females is ≈50 times higher than lower percentile normal endogenous doses, ≈10-20 times higher than median and upper percentile endogenous doses, and >26,000-37,000 times higher than that associated with typical environmental EtO levels (i.e., background and environmental means of 0.0044-0.0062 µg/m^3 (USEPA 2016) = 0.0024-0.0034 ppb × 70 years × 365 days/year = 61.32-86.87 ppb-days = 0.06132-0.08687 ppm-days).

In summary, high occupational EtO exposure being necessary to produce statistical increases in cancer in the NIOSH cohort, especially in conjunction with null results reported from the UCC cohort (with follow-up through 2013), is not supportive of the steep slope of an overall supra-linear dose-response beginning just above zero dose (e.g., at lower and more environmentally-relevant exposures). *More specifically, risk at endogenous background level doses of EtO (and below) is not expected to be consistent with the lower steep slope portion of an overall supra-linear model (e.g., USEPA's linear two-piece spline model) considering: (1) carcinogenic EtO doses based on the NIOSH study are orders of magnitude higher than normal background endogenous doses in the unexposed population (Tables 4 and 5); (2) USEPA's expectation of sublinearity in the endogenous range, which the TCEQ generally agrees with based on MOA considerations (see Section 3.4.1.1); and (3) the overall study results for both the NIOSH and UCC cohorts in workers exposed to extraordinarily high air concentrations/doses of EtO (e.g., negative findings from the UCC cohort; no statistically increased cancer in the lower NIOSH exposure groups that were still subjected to extraordinarily high air concentrations/doses).* In regard to the steep low-dose slope of an overall supra-linear dose-response being inconsistent with cohort findings on EtO-induced carcinogenicity, **the next section demonstrates the statistically significant over-estimation of risk from EtO exposure for the NIOSH cohort by USEPA's selected model assessment (i.e., the upper bound on the linear two-piece spline model) for both total lymphoid cancer mortalities in the cohort as well as for every exposure quintile.**

Table 4: Occupational Exposures Corresponding to Normal Background Endogenous Levels of EtO versus Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort (Valdez-Flores et al. 2010)

Statistically Increased Cancer Mortality Endpoint in NIOSH Cohort (sex-specific)	Environmental Exposures Corresponding to Normal Background Endogenous EtO Levels (ppm-days) [a]	Occupational Exposures Equivalent to Environmental Exposures Corresponding to Endogenous EtO Levels (ppm-days) [b]	Occupational Exposure Interval for Lowest Quantile with Statistically Elevated Risk (ppm-days) [c]	Carcinogenic Dose Compared to Normal Endogenous EtO Background Levels
Lymphohematopoietic (statistically increased in males, not females) [d]	48.5 (mean) 40.9 (median) 14.3 (5th percentile) 115.0 (95th percentile)	147.7 124.3 43.5 349.7	≥70,223.59 (highest (5th) quantile)	≥475.6 times ≥564.8 times ≥1,613.6 times ≥200.8 times
Lymphoid Tumors (statistically increased in males, not females) [d]	48.5 (mean) 40.9 (median) 14.3 (5th percentile) 115.0 (95th percentile)	147.7 124.3 43.5 349.7	≥88,348.10 (highest (5th) quantile)	≥598.3 times ≥710.5 times ≥2,030.0 times ≥252.6 times
Non-Hodgkin's Lymphoma (statistically increased in males, not females) [d]	48.5 (mean) 40.9 (median) 14.3 (5th percentile) 115.0 (95th percentile)	147.7 124.3 43.5 349.7	≥117,018.15 (highest (5th) quantile)	≥792.5 times ≥941.1 times ≥2,688.8 times ≥334.6 times
Breast Cancer (*not statistically increased* in females)	48.5 (mean) 40.9 (median) 14.3 (5th percentile) 115.0 (95th percentile)	147.7 124.3 43.5 349.7	≥14,959.26 (highest (5th) quantile)	≥101.3 times ≥120.3 times ≥343.9 times ≥42.8 times
		Carcinogenic Dose [e] Average Magnitude of Exceedance Over Normal Background Levels at the Endogenous:	**mean median 5th percentile 95th percentile**	**≥622.1 times ≥738.8 times ≥2,110.8 times ≥262.7 times**

[a] Environmental exposure (ppm-days) corresponding to normal endogenous = continuous air concentrations of 0.0019, 0.0016, and 0.00056-0.0045 ppm corresponding to the mean, median, and 5^{th}-95^{th} percentile range for normal endogenous HEV levels in the unexposed (Table 4 of Kirman and Hays 2017) × 70 years × 365 days/year.
[b] Occupational exposure equivalent to environmental (ppm-days) = environmental (ppm-days) × 20 m^3/10 m^3 × 365 days/240 days (i.e., a multiplicative factor of ≈3.042; unrounded values used for calculations); see footnote "2" to Table S.12 of Valdez-Flores et al. (2010).
[c] Table S.9 of Valdez-Flores et al. (2010): Rate ratio analyses and Cox proportional hazards model for cumulative exposure for each combination of endpoint, sex, and study; note that breast cancer was not statistically increased in the rate ratio analysis of Valdez-Flores et al. (2010).
[d] Not statistically elevated in females, only males, so male + female combined results not provided as any risk is driven by the dose-response in males (e.g., statistically significant increases for lymphoid tumors and non-Hodgkin's lymphoma in males + females combined but not in females alone, only males).
[e] These comparisons exclude breast cancer as it was not statistically increased in the rate ratio analyses of Valdez-Flores et al. (2010).

Table 5: Occupational Exposures Corresponding to Normal Background Endogenous Levels of EtO versus Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort (Steenland et al. 2004, 2003)

Statistically Increased Cancer Endpoint in NIOSH Cohort (sex-specific)	Environmental Exposures Corresponding to Normal Background Endogenous EtO Levels (ppm-days) [a]	Occupational Exposures Equivalent to Environmental Exposures Corresponding to Endogenous EtO Levels (ppm-days) [b]	Occupational Exposure Interval for Lowest Quantile with Statistically Elevated Risk (ppm-days)[c]	Carcinogenic Dose Compared to Normal Endogenous EtO Background Levels
All Hematopoietic (statistically increased in males, not females) [d]	48.5 (mean) 40.9 (median) 14.3 (5th percentile) 115.0 (95th percentile)	147.7 124.3 43.5 349.7	≥13,500 (highest (4th) quantile, 15-yr lag)	≥91.4 times ≥108.6 times ≥310.3 times ≥38.6 times
Lymphoid Cell Line Tumors (statistically increased in males, not females) [d]	48.5 (mean) 40.9 (median) 14.3 (5th percentile) 115.0 (95th percentile)	147.7 124.3 43.5 349.7	≥13,500 (highest (4th) quantile, 15-yr lag)	≥91.4 times ≥108.6 times ≥310.3 times ≥38.6 times
Non-Hodgkin's Lymphoma (statistically increased in males, not females) [d]	48.5 (mean) 40.9 (median) 14.3 (5th percentile) 115.0 (95th percentile)	147.7 124.3 43.5 349.7	≥13,500 (highest (4th) quantile, 10-yr lag)	≥91.4 times ≥108.6 times ≥310.3 times ≥38.6 times
Breast Cancer (incidence in females)	48.5 (mean) 40.9 (median) 14.3 (5th percentile) 115.0 (95th percentile)	147.7 124.3 43.5 349.7	>14,620 (highest (5th) quantile, 15-yr lag)	>99.0 times >117.6 times >335.9 times >41.8 times
		Carcinogenic Dose Average Magnitude of Exceedance Over Normal Background Levels at the Endogenous:	**mean median 5th percentile 95th percentile**	**≥93.3 times ≥110.9 times ≥316.7 times ≥39.4 times**

[a] Environmental exposure (ppm-days) corresponding to normal endogenous = continuous air concentrations of 0.0019, 0.0016, and 0.00056-0.0045 ppm corresponding to the mean, median, and 5^{th}-95^{th} percentile range for normal endogenous HEV levels in the unexposed (Table 4 of Kirman and Hays 2017) × 70 years × 365 days/year.
[b] Occupational exposure equivalent to environmental (ppm-days) = environmental (ppm-days) × 20 m^3/10 m^3 × 365 days/240 days (i.e., a multiplicative factor of ≈3.042; unrounded values used for calculations); see footnote "2" to Table S.12 of Valdez-Flores et al. (2010).
[c] Tables 4, 6, and 7 of Steenland et al. (2004) and Table 4 of Steenland et al. (2003).
[d] Not statistically elevated in females or females + males, only males.

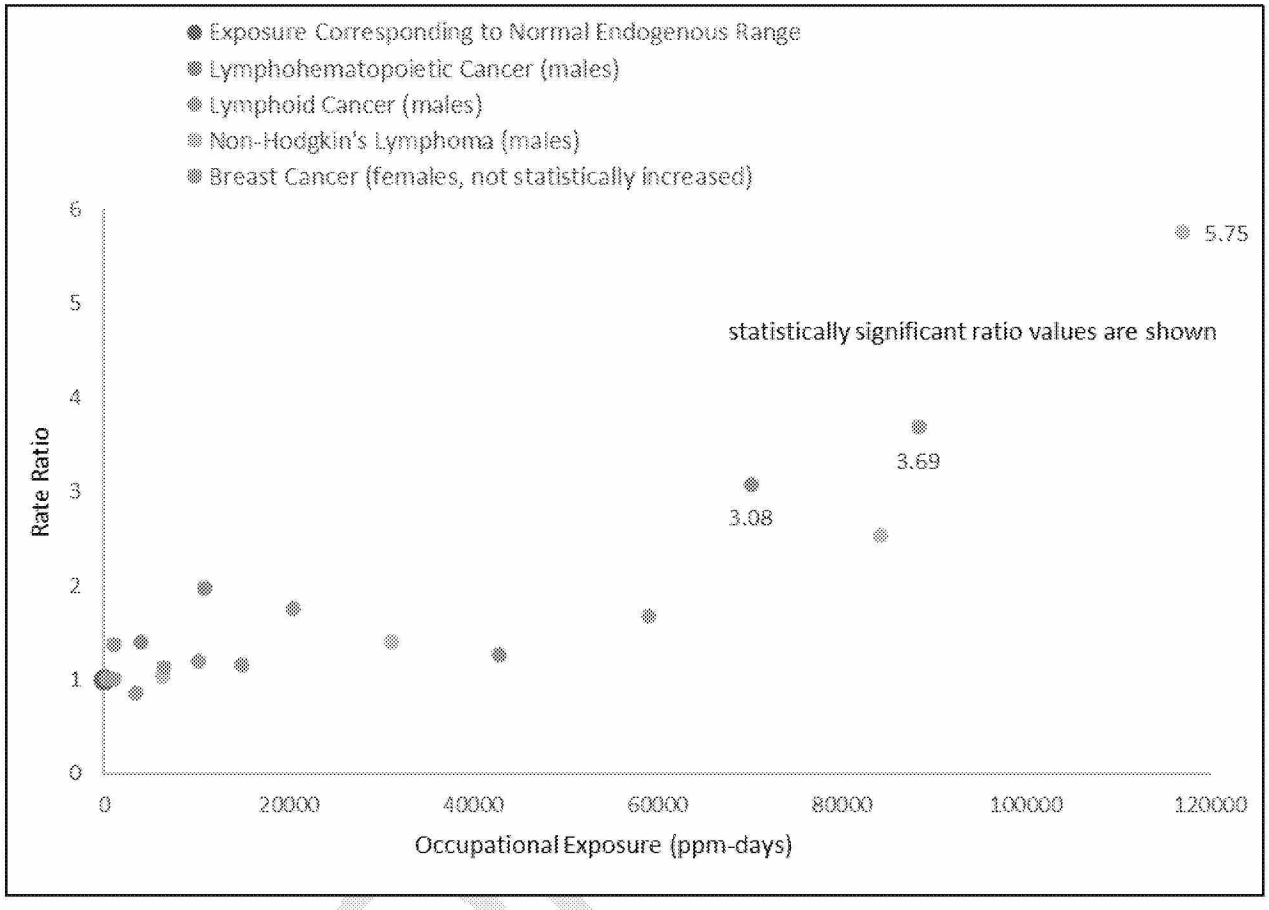

Figure 2: Occupational Exposures Corresponding to Normal Background Endogenous Levels of EtO versus Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort - Linear Scale

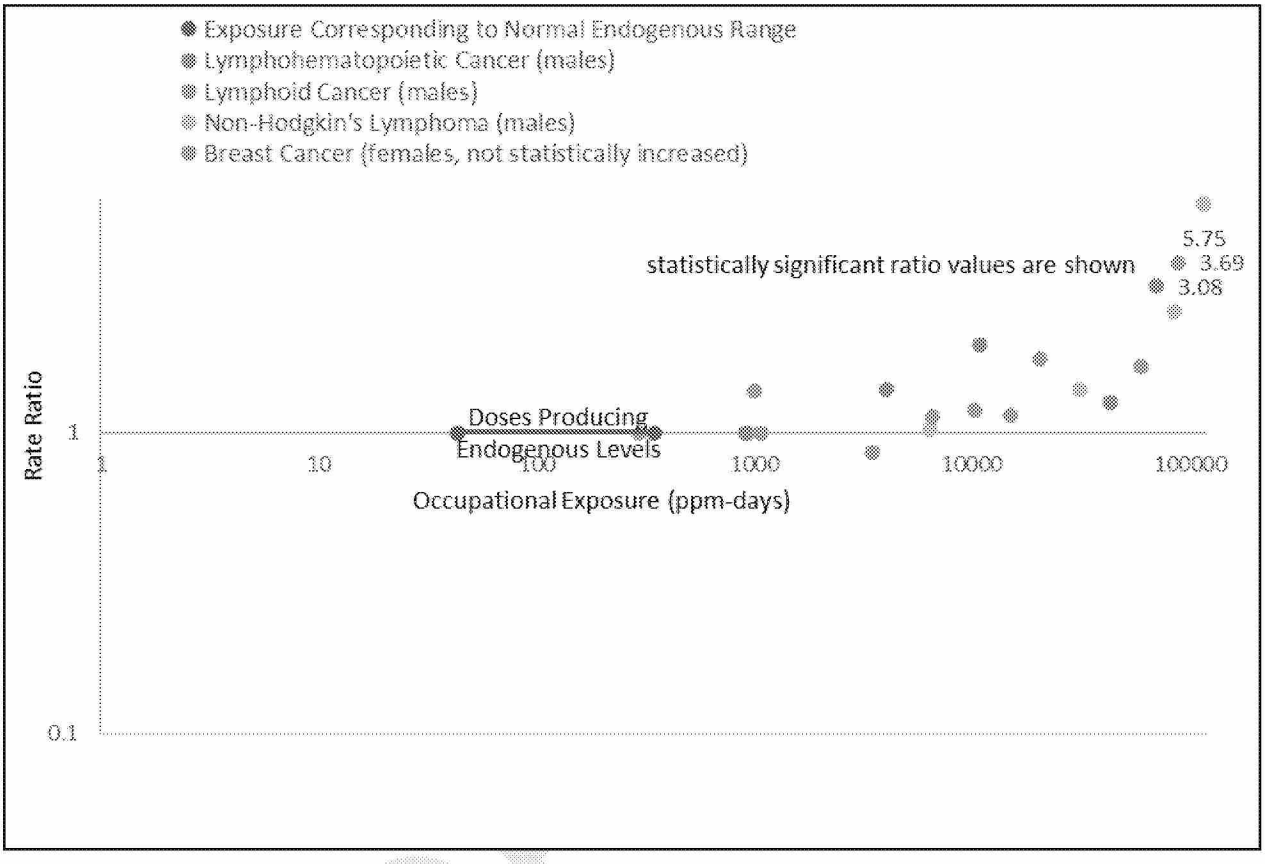

Figure 3: Occupational Exposures Corresponding to Normal Background Endogenous Levels of EtO versus Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort - Log Scale

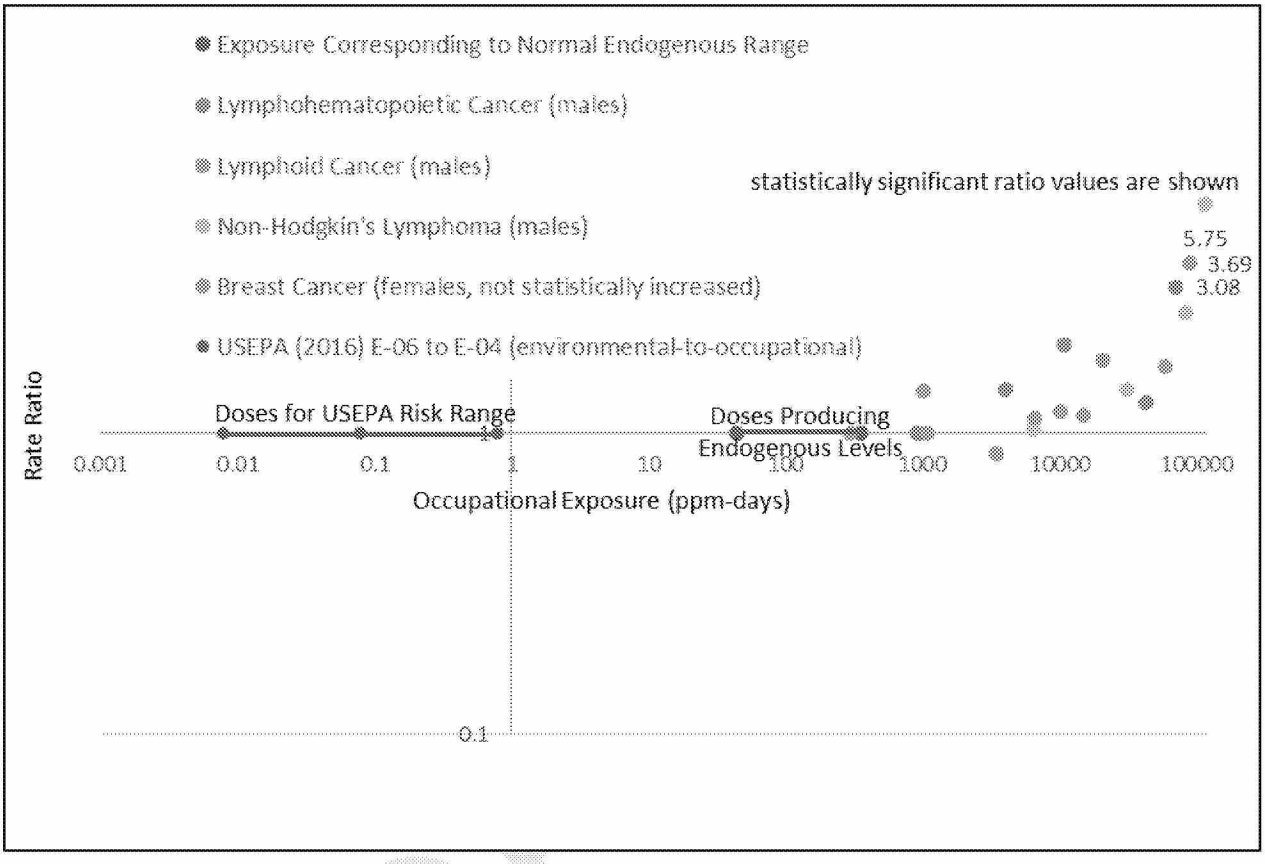

Figure 4: Occupational Exposures Corresponding to USEPA Risk-Based Doses and Normal Background Endogenous Levels of EtO versus Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort - Log Scale

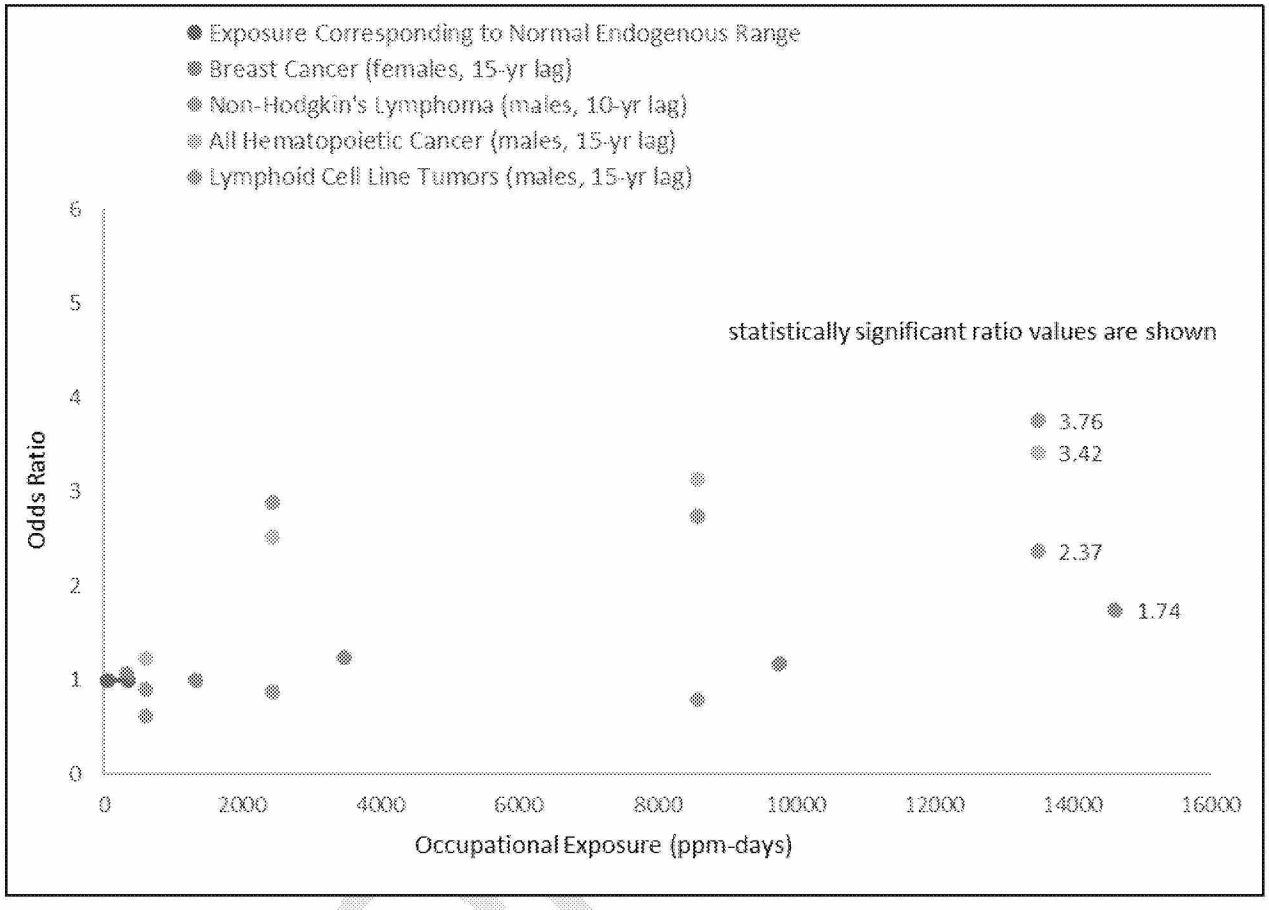

Figure 5: Occupational Exposures Corresponding to Normal Background Endogenous Levels of EtO versus Lagged Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort - Linear Scale

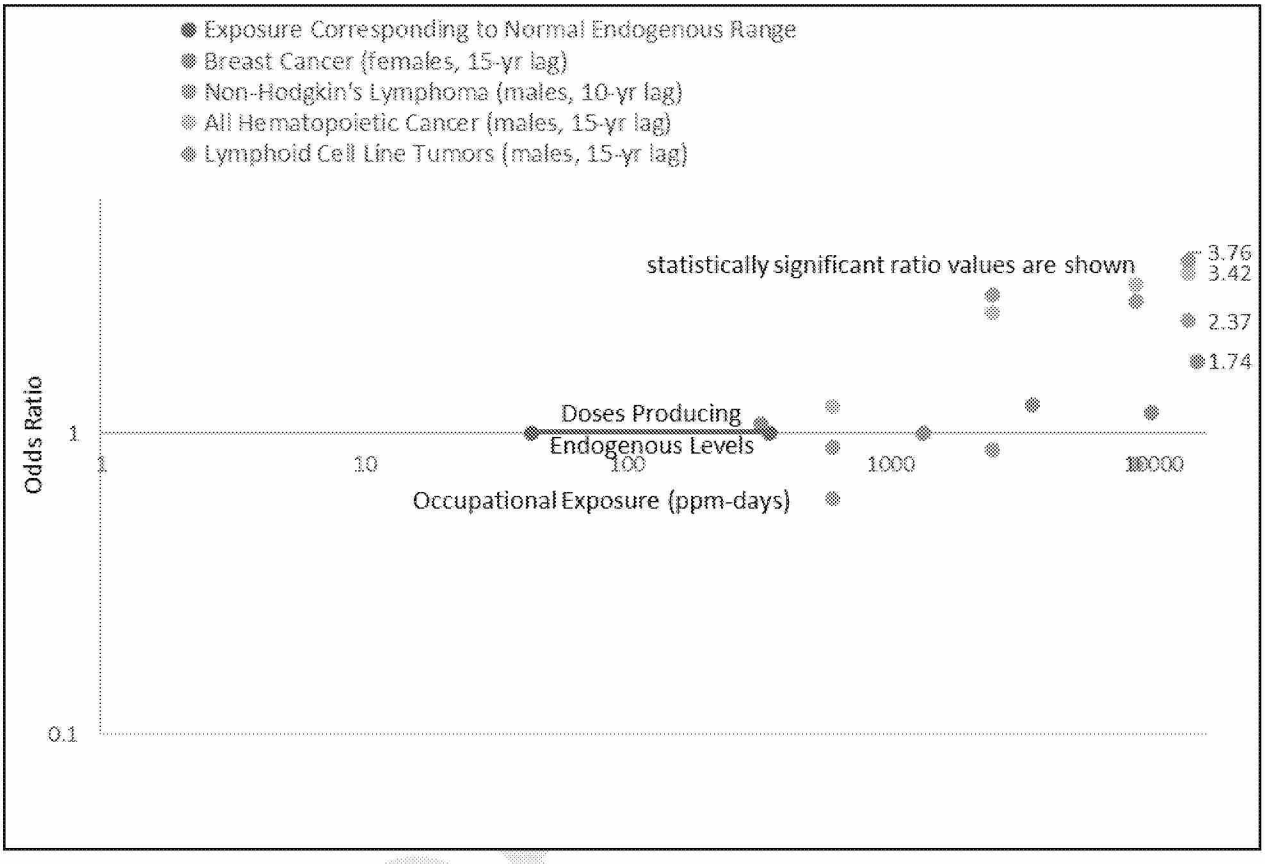

Figure 6: Occupational Exposures Corresponding to Normal Background Endogenous Levels of EtO versus Lagged Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort - Log Scale

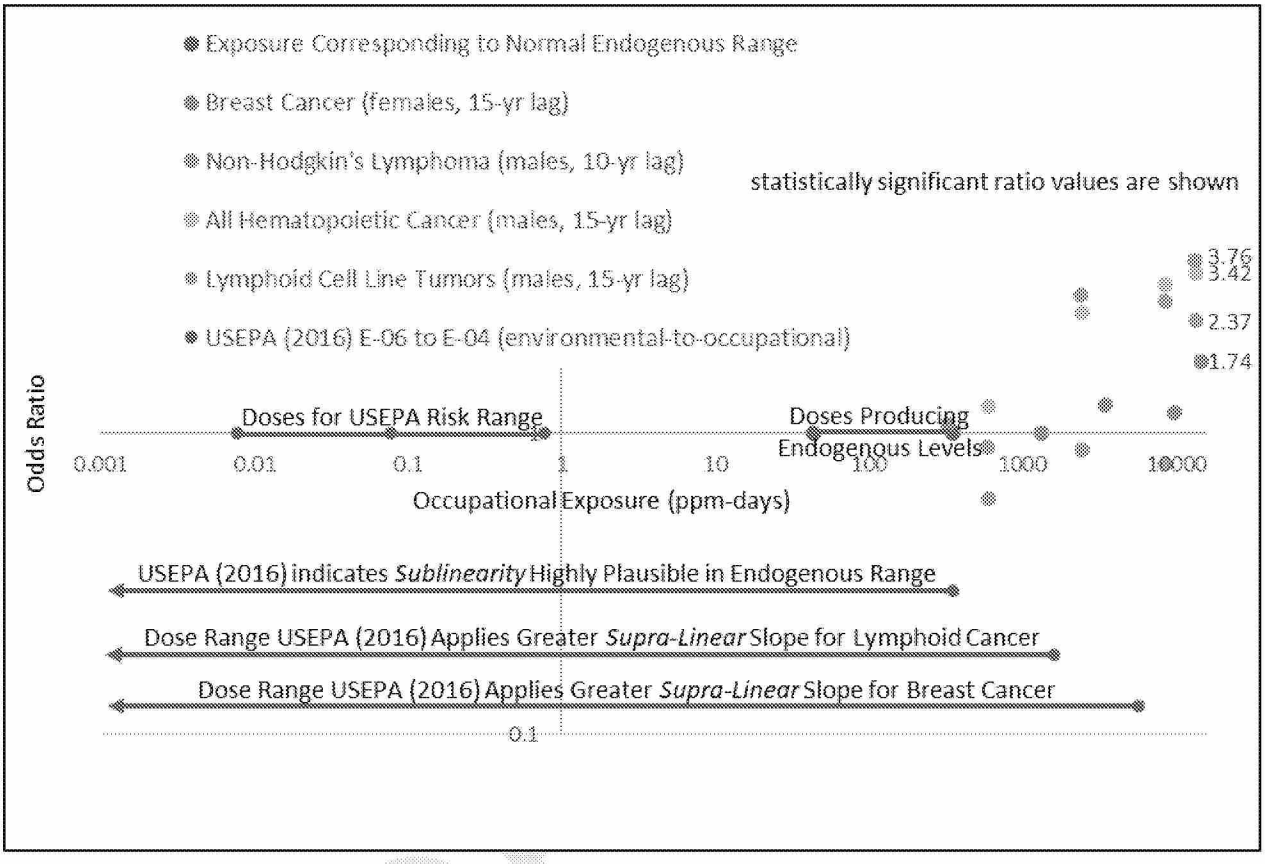

Figure 7: Occupational Exposures Corresponding to USEPA Risk-Based Doses and Normal Background Endogenous Levels of EtO versus Lagged Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort - Log Scale

3.4.1.2.2.3 Lymphoid Cancer in the NIOSH Cohort - Model Predictions Versus Observed

To ground-truth USEPA and other EtO dose-response models (e.g., USEPA's selected assessment of the upper bound on the linear two-piece spline model), the various models were used to estimate the number of lymphoid cancer deaths predicted to occur at the EtO exposure levels estimated for the NIOSH cohort compared to the number of cancer deaths that were actually observed in that cohort (details in Appendix 3). This model ground-truthing exercise demonstrated that *statistically significant increases in lymphoid cancer mortality would have been observed in every cumulative exposure group beginning in the lowest EtO exposure group of the NIOSH cohort if the model assessment selected by USEPA (i.e., the upper bound of the linear two-piece spline model with the "knot" at 1,600 ppm × days, 15-year exposure lag) were realistic (Table 32 of Appendix 3). In addition, USEPA's selected model assessment predicts that a total of 141 lymphoid cancer deaths (95% CI of 108 to 188) would be expected with the EtO exposure levels estimated for the NIOSH cohort (Table 31 of Appendix 3). However, only 53 total deaths from lymphoid cancers were actually observed, demonstrating that USEPA's selected model assessment statistically significantly over-estimates risk.* By contrast, the model assessment ultimately selected by the TCEQ (i.e., the upper bound on the Cox proportional hazards model, 15-year exposure lag; see Section 3.4.1.4.2) is reasonably accurate, predicting 59 lymphoid cancer mortalities from EtO exposure compared to the 53 actually observed (Figure 8).

For quintile-specific results (Table 32 of Appendix 3), the model analysis demonstrated that *for every cumulative EtO exposure group, the linear two-piece spline model assessment utilized by USEPA (2016) statistically significantly over-predicts the 11 lymphoid cancer mortalities that actually occurred in each quintile.* Further, the predictions by the model assessment selected by USEPA (2016) demonstrate that *if the model were realistic, then statistically significant lymphoid cancer increases would have occurred in every cumulative EtO exposure quintile beginning in the lowest (i.e., the lower ends of the 95% CIs range from 17-20 lymphoid cancer mortalities, compared to the 9 lymphoid cancer mortalities in the controls).* These predictions by USEPA's selected model assessment are not borne out by the observed cohort data. On the other hand, the log-linear (Cox proportional hazards) model that is ultimately chosen by the TCEQ (see Section 3.4.1.4.2) does not significantly over- or under-predict the lymphoid cancer deaths observed in any NIOSH cumulative EtO exposure group (Figures 9-12).

In accordance with the discussions above, *the application of the model assessment selected by USEPA (i.e., the upper bound of the linear two-piece spline model with the "knot" at 1,600 ppm × days, 15-year exposure lag) results in statistically erroneous over-predictions of lymphoid cancer risk for the very cohort the model is supposed to fit.* The model is erroneous for the cohort as a whole and every cumulative exposure group, and the URF derived from it lacks the scientific credibility required for regulatory agency use for this and other reasons described in other sections of this DSD (i.e., the lack of mechanistic justification and other considerations).

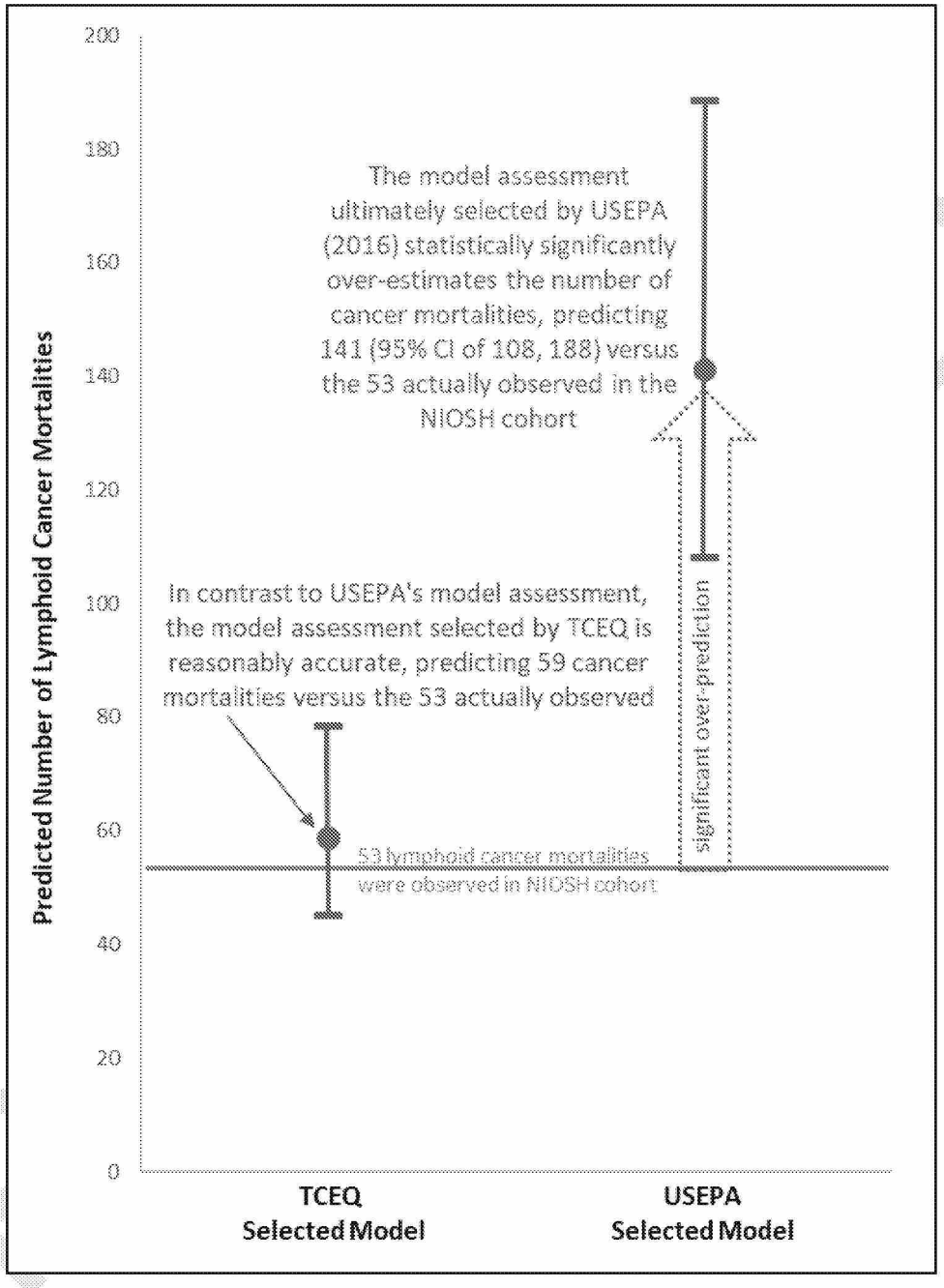

Figure 8: Statistically Significant Over-Prediction of Lymphoid Cancer Mortalities from EtO Exposure by the USEPA (2016) Selected Model Assessment (upper bound of linear two-piece spline) for the NIOSH Cohort versus Reasonably Accurate Results from the TCEQ Selected Model (upper bound Cox proportional hazards)

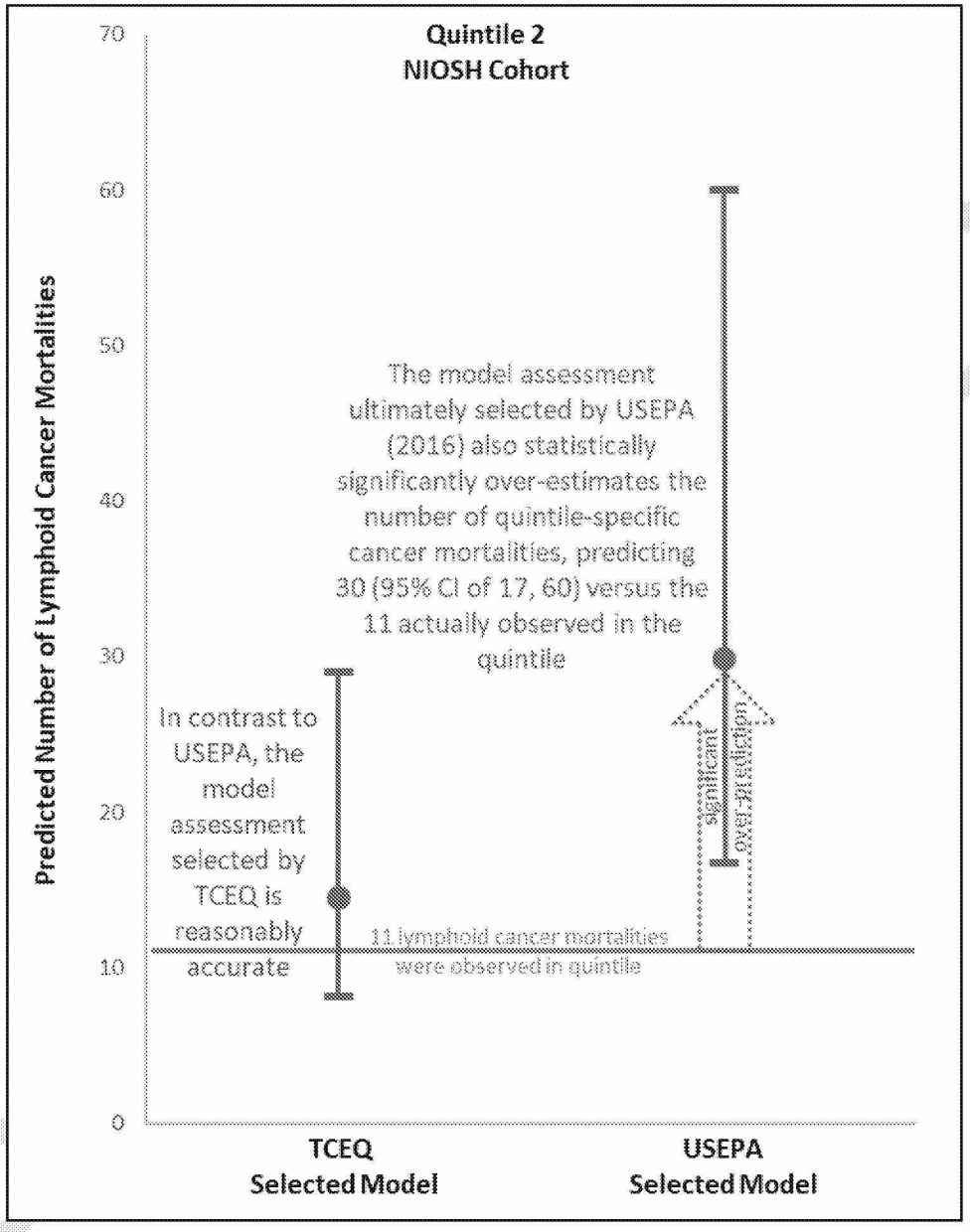

Figure 9: Statistically Significant Over-Prediction of Lymphoid Cancer Mortalities from EtO Exposure by the USEPA (2016) Selected Model Assessment (upper bound of linear two-piece spline) for the NIOSH Cohort versus Reasonably Accurate Results from the TCEQ Selected Model (upper bound Cox proportional hazards) - Quintile 2

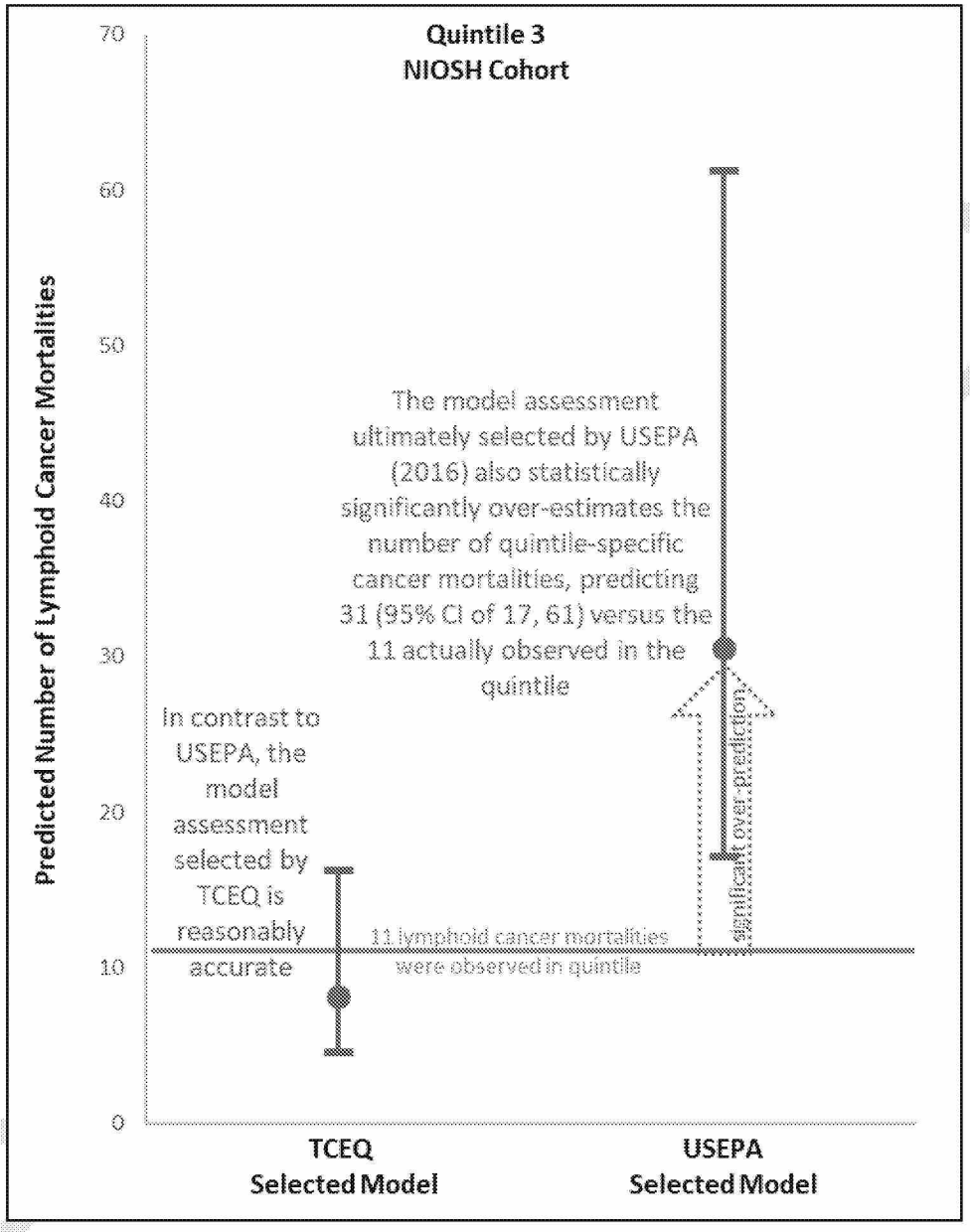

Figure 10: Statistically Significant Over-Prediction of Lymphoid Cancer Mortalities from EtO Exposure by the USEPA (2016) Selected Model Assessment (upper bound of linear two-piece spline) for the NIOSH Cohort versus Reasonably Accurate Results from the TCEQ Selected Model (upper bound Cox proportional hazards) - Quintile 3

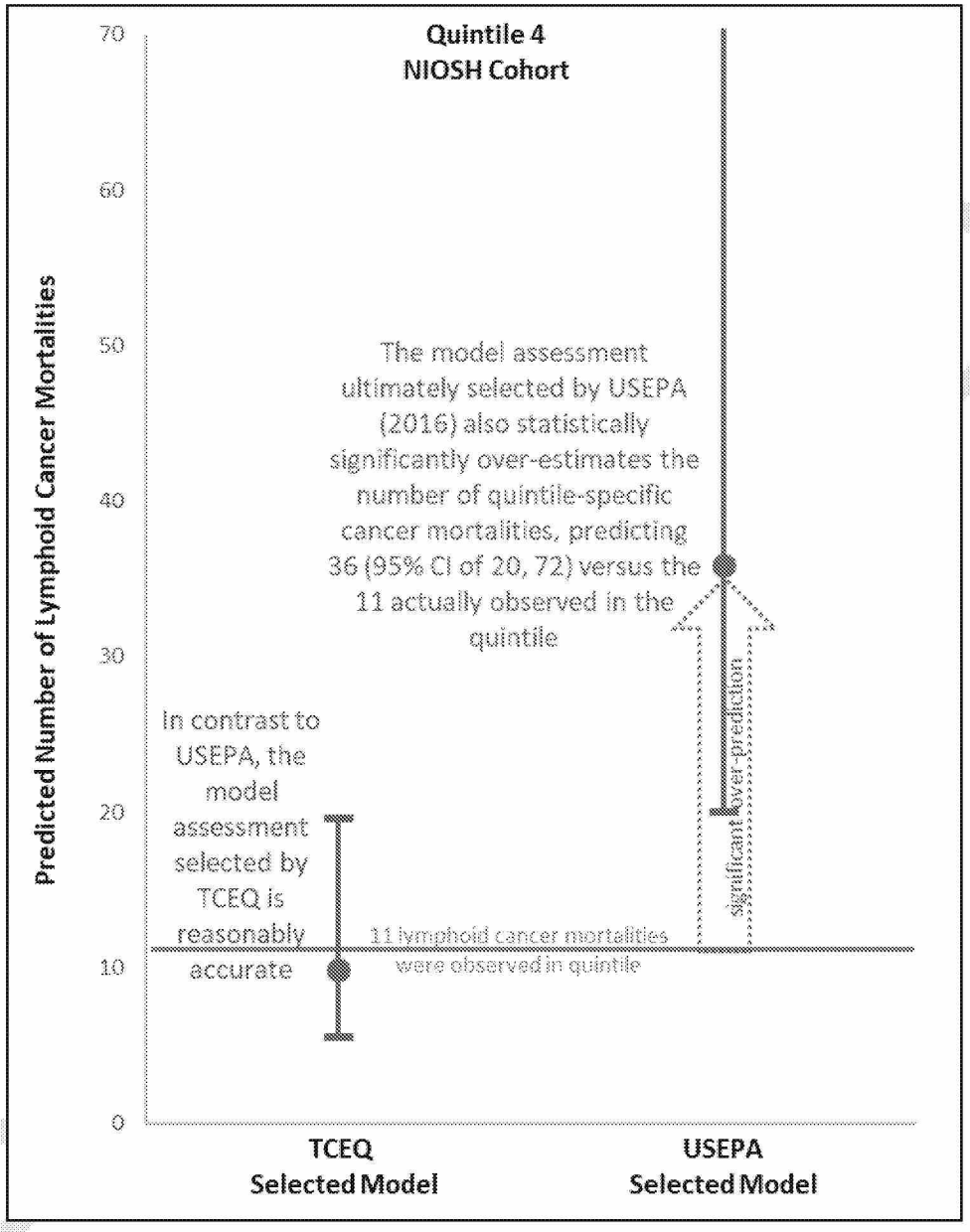

Figure 11: Statistically Significant Over-Prediction of Lymphoid Cancer Mortalities from EtO Exposure by the USEPA (2016) Selected Model Assessment (upper bound of linear two-piece spline) for the NIOSH Cohort versus Reasonably Accurate Results from the TCEQ Selected Model (upper bound Cox proportional hazards) - Quintile 4

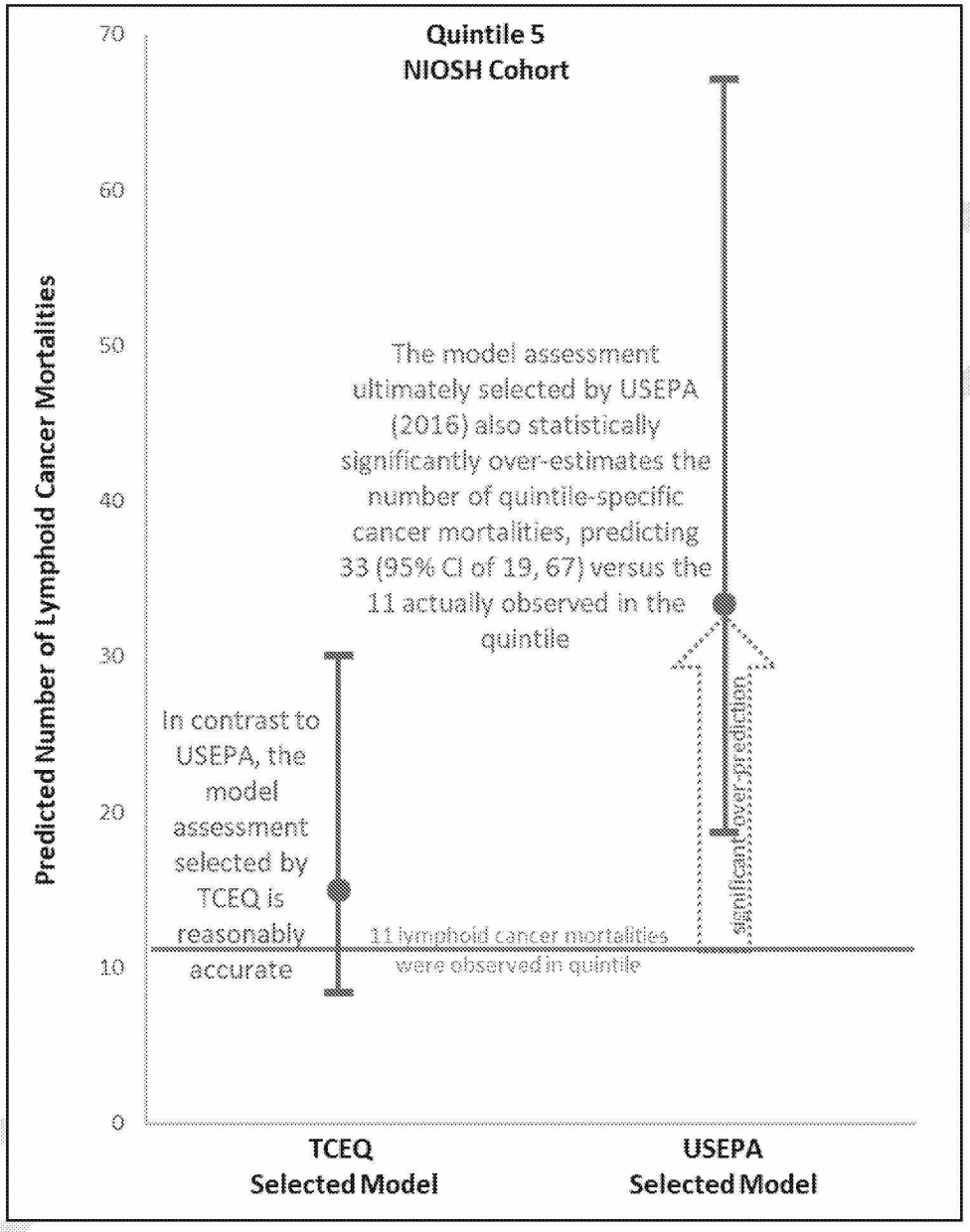

Figure 12: Statistically Significant Over-Prediction of Lymphoid Cancer Mortalities from EtO Exposure by the USEPA (2016) Selected Model Assessment (upper bound of linear two-piece spline) for the NIOSH Cohort versus Reasonably Accurate Results from the TCEQ Selected Model (upper bound Cox proportional hazards) - Quintile 5

3.4.1.2.2.4 Implications of Key Epidemiological Findings, Endogenous Data, and Model Predictions for Use of USEPA's Selected Linear Two-Piece Spline Model Assessment and URF

In summary, the consideration of key epidemiological data such as findings for the UCC and NIOSH cohorts, the carcinogenic doses associated with critical cancer endpoints in the NIOSH study, doses corresponding to normal background endogenous levels, as well as demonstrations of statistically significant over-prediction by USEPA's selected linear two-spline model assessment for lymphoid cancer (the primary URF driver) is not supportive of a supra-linear EtO dose-response (i.e., the steep low-dose slope portion), particularly for low-dose extrapolation (e.g., within or below the range of normal endogenous and ambient levels). Regarding the endogenous range, USEPA (2016) considers it "*highly plausible that the dose-response relationship over the endogenous range is sublinear*." Despite this, as shown in Figure 7, USEPA (2016) actually applied exceptionally steep low-dose slopes from overall supra-linear models for lymphoid and breast cancer in the very low-dose region where a sublinear dose-response is expected (i.e., the endogenous range and even lower). The TCEQ contends that USEPA's choice and application of an overall supra-linear EtO dose-response relationship is therefore internally inconsistent (i.e., self-contradictory). Moreover, the TCEQ has determined that USEPA's use of a supra-linear dose-response (i.e., in particular the steep low-dose slope portion) for low-dose extrapolation is contrary to other considerations discussed above and is not scientifically defensible. *Among other considerations, as part of the scientific weight of evidence, the demonstration of the statistically significant over-estimation of lymphoid cancer risk by the model assessment selected by USEPA (i.e., the upper bound of the linear two-piece spline model with the "knot" at 1,600 ppm × days, 15-year exposure lag), compared to the observed number of lymphoid cancer deaths in the cohort, indicates that this model is not appropriate for deriving the EtO URF.*

[As a peripherally-related topic, the inability to observe sublinearity in the NIOSH cohort might be explained by the lack of dose-response data at low air concentrations (e.g., a few ppb) that would allow total internal exposures (endogenous + exogenous) to remain in/near the normal endogenous range. See Figures 3 and 6, keeping in mind that the exogenous exposures corresponding to the normal background endogenous range would themselves produce internal exposures equal to endogenous exposures, over and above them (and that occupational exposures in Figure 6 have been artificially reduced by lagging exposure 10-15 years). Thus, the available dose-response data appear predominated by exposures above the area in the dose-response expected to be sublinear (i.e., within/near/below the normal endogenous range). In such a case, if the available data are at doses sufficiently high to be in the area of the dose-response where disproportionally increased risk occurs, then the dose-response observed based on the data available might be expected to appear supra-linear overall. Other than providing a hypothetical example in Appendix 4, the TCEQ has not evaluated this possibility further as it is somewhat beyond the scope of this DSD.]

3.4.1.3 Consideration of Model Fit Criteria

Although some models have a biological or mechanistic basis (e.g., Michaelis-Menten model of enzyme kinetics, CIIT biologically-based model for formaldehyde), many models used for dose-response assessment do not (e.g., often only to the extent that low-dose linearity is viewed as consistent with a mutagenic MOA). Thus, model fit is a much lesser consideration compared to the consideration of any data that may (or may not) adequately support use of a supra-linear model (TCEQ 2015). For example*, neither USEPA nor TCEQ can cite mechanistic data for EtO that sufficiently support use of a supra-linear model, particularly in the context of concerns about the steepness of the linear two-piece spline model slope over the low-dose region* (e.g., USEPA 2016 considers *sublinearity* "highly plausible" over the endogenous range). In fact, relevant considerations support that the steep low-dose of a supra-linear model should not be used over the low-dose region in this case (see Sections 3.4.1.1 and 3.4.1.2). However, model fit is nevertheless a topic of interest for EtO and therefore the topic is discussed, albeit not as a deterministic consideration. This section focuses on lymphoid cancer because it was the primary driver of the USEPA (2016) URF, although model fit for breast cancer incidence is also considered. In TCEQ's evaluation of dose-response models that provide the most appropriate fit to the EtO cohort data, the agency also evaluated USEPA's application of model fit criteria to determine if appropriate for use by the TCEQ.

There are two important overarching issues with USEPA's consideration of model fit and ultimate selection of the linear two-piece spline model that the TCEQ must duly consider. The first concerns the statistical optimization of "knot" values for the two-piece spline modeling approach. USEPA (2016) indicates that for this approach, the splines were "fit" to the EtO cancer exposure-response data, and that the knot was generally selected by evaluating different knots in increments (e.g., 100, 500, or 1,000 ppm × days) of cumulative exposure and then by choosing the one that resulted in the best (i.e., largest) model likelihood (pp. 4-13, 4-26, 4-36, and 4-45 of USEPA 2016). Thus, from the process described, it is readily apparent that:

- The "knot" was an iteratively fit model parameter and not simply "preselected" (p. 4-52 of USEPA 2016); and
- The knot values, *being statistically estimated/optimized based on the NIOSH data*, clearly do not conform to the USEPA SAB's notion of potentially fixing some model parameters *not estimated from the data* in the interest of parsimony (see p. 12 of SAB 2015).

"Preselected" is a somewhat ambiguous term that does not adequately characterize and obfuscates how the knot value was statistically fit. This is an important procedural/methodological issue as it appears that under USEPA's interpretation, multiple model parameters could be statistically estimated/optimized upstream of a final dose-response model, yet none of the fitted parameters would ultimately count as an estimated (k) parameter